Journal Club

Too much hypothalamic serotonin transporter is bad for your mood

The working hypothesis for the biochemical basis of depression – a disabling mood disorder affecting at least 1% of the adult population – is that there is a lasting deficiency of available serotonin in brain regions that control mood. This notion is supported by observations that the most effective anti-depressant drugs, fluoxetine, paroxetine and fluvoxamine, are potent competitive inhibitors of the serotonin transporter (ST), blocking its action at sub-nanomolar concentrations. ST is a transmembrane protein responsible for terminating synaptic serotonin signaling by re-uptake of the released neurotransmitter to the presynaptic terminals. Thus, common wisdom holds that anti-depressant drugs improve mood by blocking the action of synaptic ST, thereby increasing the duration of action of serotonin following its synaptic release.

It was long suspected that the reduced brain serotonin availability in depressed patients reflected overexpression of the ST gene or underexpression of genes encoding serotonin-synthesizing enzymes or for certain serotonin receptor subtypes. However, clear conclusions were not available from post-mortem human tissues, since depressive patients are usually on medication for long periods. This, combined with the lack of good animal models for human depression, meant that there were no clear answers. Now, a new study from the Clinic of Child Psychiatry at the University of Oulu, Finland[1], reports that hypothalamic/midbrain ST levels in drug-naive depressed children and adolescents are elevated compared with non-depressed patients. The study employed ^{123}I-labeled β-CIT, which strongly binds ST and can be visualized *in vivo* using single photon emission computerized tomography (SPECT). Such measurements indicated that 24 h following tracer injection, hypothalamic/midbrain ST labeling was 22% higher in depressive patients – a difference seen in both male and female patients.

This is the first demonstration of elevated *in vivo* brain ST levels in depressed humans. Hence, it strongly supports the rationale for using ST blockers as treatment for depression. Notably, a recent study shows that depressed patients differ in their response to anti-depressant drugs depending on their ST promoter genotype, with patients having two copies of the longer ST promoter allele showing improved drug efficacy[2]. Apparently, in these patients the limbic ST levels are even higher compared with other depressive patients, or alternatively, more effectively downregulated by anti-depressant drugs. It remains to be seen if such correlations can be visualized *in vivo* using SPECT.

References
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2 Pollock, B.G. *et al.* (2000) Allelic variation in the serotonin transporter promoter affects onset of paroxetine treatment response in late-life depression. *Neuropsychopharmacology* 23, 587–590

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Pseudohypoparathyroidism: new insight into $G_s\alpha$

Pseudohypoparathyroidism (PHP) is an endocrinopathy characterized by resistance to parathyroid hormone (PTH) in target tissues, resulting in hypocalcaemia and hyperphosphataemia despite increased secretion of PTH. PHP is subclassified according to additional biochemical and clinical criteria. In PHP type Ia, patients commonly show resistance to thyroid stimulating hormone (TSH) and luteinizing hormone (LH), as well as to PTH, and have clinical features known as Albright hereditary osteodystrophy (AHO) characterized by round faces, short stature and shortened fingers and toes. At the molecular level, PHPIa is known to result from heterozygous inactivating mutations in the gene GNAS1, which encodes the α-subunit of the heterotrimeric G-protein, G_s. G_s couples the receptors for various hormones, including PTH, TSH and LH, to activation of intracellular adenylyl cyclase. Patients with PHPIa show a 50% reduction in $G_s\alpha$ activity in their cell membranes.

By contrast, PHP type Ib is characterized by isolated resistance to PTH, normal $G_s\alpha$ activity and absence of AHO. It was originally hypothesized that PHPIb would result from mutations of the PTH receptor gene, but extensive analysis failed to confirm this. Recently, PHPIb was localized to a region of chromosome 20 very close to GNAS1. Wu *et al.*[1] now describe an intriguing novel mutation in GNAS1 that leads to PHPIb rather than PHPIa. The mutation was identified in three affected brothers and results in deletion of one amino acid at the C-terminus of $G_s\alpha$, a region important for receptor interaction. *In vitro* expression assays confirmed that the mutation selectively uncouples $G_s\alpha$ from the PTH receptor without affecting its interaction with receptors for TSH or LH, thus explaining the PTH-specific phenotype. The mutation was not found in 15 additional unrelated patients and is therefore not a common cause of PHPIb. Other possible mechanisms include promoter mutations with tissue-specific effects, or mutations in alternative $G_s\alpha$ transcripts. GNAS1 is already known to be a complex imprinted locus and this report underlines the molecular complexities of $G_s\alpha$ expression and function.

References
1 Wu, W-I. et al. Selective resistance to parathyroid hormone caused by a novel uncoupling mutation in the carboxyl terminus of $G_s\alpha$: a cause of pseudohypoparathyroidism type Ib. *J. Biol. Chem.* (in press) http://www.jbc.org/cgi/reprint/M006032200v1

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